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Facultad de Medicina
Departamento de Enfermedades Infecciosas e Inmunología Pediátrica
Facultad de Ciencias Biológicas
Departamento de Genética Molecular y Microbiología

PROTOCOL TITLE:

Multi-center, phase 3, double blind, placebo-controlled, randomized study to evaluate the efficacy, safety and immunogenicity of an inactivated vaccine against the SARS-CoV-2 infection in high risk of infection adults.

Protocol short name:	Coronavac03CL
Version N°:	5.0
Date:	23th October 2020
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Scientific Director:	Dra. Susan Bueno
Sponsoring Institution:	Pontificia Universidad Católica de Chile. Avda. Libertador Bernardo O´Higgins 340, Santiago, Chile Non profit institution, educational
Funding Source:	Government and private funding
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1. Background

Sinovac Life Sciences Co., Ltd. (Beijing, China) has worked in developing an inactivated SARS-CoV-2 vaccine since January 2020 in partnership with leading academic research institutes in China. The Company received approval from China's NMPA on April 13 to conduct phase I/II studies on its inactivated vaccine candidate against COVID-19 in China, after having demonstrated that the vaccine was safe and immunogenic in different animal models, including mice and non-human primates (Gao et al, Science 2020).

The phase I/II clinical trials were designed as randomized, double-blind and placebo-controlled studies. In total, 743 healthy volunteers, aged from 18 to 59 years old, enrolled in the trials. Of those, 143 volunteers participated in phase I and 600 volunteers in phase II. There was no severe adverse event (SAE) related to the vaccine reported in phase I/II trials. The phase II clinical trial results show that the vaccine induces neutralizing antibodies 14 days after the vaccination with a 0-14-day schedule. The neutralizing antibody seroconversion rate is above 90%, which concludes the vaccine candidate can induce positive immune response. The vaccination schedule determined in those studies will be two doses of 600 Standard Units (SU)/0,5 mL, separated by 14 days (Zang et al, medRixv, 2020).

Considering the worldwide situation of the SARS-CoV-2 pandemic, it is necessary to promptly carry out multicenter clinical studies with vaccines that have completed phase 2 studies. The proposed study will allow efficacy assessment in a country with high level of viral circulation and different genetic population background than the Chinese population. Phase III clinical trials with this vaccine started in Brazil (Butantan Institute) in August, 2020 and it is planned to be done in other countries apart from Chile (Indonesia, Saudi Arabia, Philippines, Bangladesh and Turkey) since October 2020. At the time of this version of the protocol, it is planned to conduct the joint efficacy and safety analysis between Chile and Brazil.

High-risk population to acquire the infection, as health personnel who works in hospitals attending COVID19 patients will be the target population for this study. In Chile, the rate of infection at mid-June is 997 cases/100,000 habs. (~1%), and in the Metropolitan Region of 1,600/100,000 habs. (~1.6%), with 179.436 confirmed cases and a fatality rate of 1.9%. In different health institutions, around 10-20% of health workers were affected.

2. Objectives

Primary objective

- Evaluate the efficacy of the inactivated vaccine anti-SARS-CoV-2 to prevent confirmed cases of COVID-19 two weeks after the second dose of vaccination
- Describe the occurrence of solicited and unsolicited adverse events up to seven days after each dose of vaccine/placebo, stratified by age group (18-59 and 60 and more years of age)

Secondary objectives

Secondary objectives for efficacy

1. Evaluate efficacy of one dose of SARS-CoV-2 inactivated vaccine against virologically confirmed SARS-CoV-2 after 2 weeks of vaccine administration

2. Evaluate efficacy of a two-dose regimen of SARS-CoV-2 inactivated vaccine against virologically confirmed SARS-CoV-2 after 2 weeks of vaccine administration
3. Evaluate efficacy of SARS-CoV-2 inactivated vaccine against COVID19 severe cases virologically confirmed after 2 weeks of vaccine administration.
4. Evaluate efficacy of SARS-CoV-2 inactivated vaccine to prevent hospital admissions after 2 weeks of vaccine administration
5. Evaluate the efficacy of the vaccine to prevent severe COVID19 cases or deaths after 2 weeks of vaccine administration

Secondary objectives for safety

1. Determine the incidence of solicited and non-solicited adverse events that occur in the 28 days after each dose, stratified by age group (18-59 and 60 and more years of age)
2. Determine the occurrence of severe COVID19 cases in participants with at least one dose of vaccine
3. Determine the occurrence of serious adverse events (SAE) and events of special interest in participants with at least one dose of vaccine

Secondary objectives for immunogenicity

1. Assess the immune response to the vaccine in a subgroup of participants before and after the administration of each vaccine dose
2. Assess cellular immune response to the vaccine in a subgroup of participants before and two and four weeks after the administration of the second vaccine dose
3. Assess the presence of anti SARS-CoV-2 antibodies in a subgroup of participants before and two weeks after the administration of each vaccine dose

Exploratory objectives

1. Evaluate the immune response in incidental cases of COVID19, in a subgroup of participants
2. Determine seroconversion rates (%) and levels(GMT) of neutralizing antibodies induced by the vaccine in a subgroup of participants
3. Determine the level of antibodies induced by the vaccine with additional immune laboratory assays in a subgroup of participants to investigate possible immune responses related to protection, in a subgroup of participants
4. Characterize the immune response after one year since the first dose in a subgroup of participants
5. Determine possible interactions between the candidate vaccine and chronic medical conditions such as diabetes, obesity, dyslipidemia, hypertension and cardiovascular diseases

See operational definitions in Section 7.2.3

3. Study design

This is a phase 3 randomized, double blind, placebo-controlled study in adults of both sex with high risk of SARS-CoV-2 infection to be enrolled and randomly assigned into 2 groups at a ratio of 1:1 to receive 2 doses of vaccine or placebo in an interval of 14 days. All subjects will be followed-up for 12 months after the first dose.

For the study population, and adaptive design will be done: starting with 3,000 health workers in this phase and adding, if necessary, a second phase with other 2,000 high risk of infection persons (eg, more health workers, some high incidence counties inhabitants, etc.).

Study centers: the study in Chile is multicenter, with various sites in the Metropolitan Region and outside of it. Annex 1 indicates the participating centers and their responsible researchers. Enrollment will be competitive among the centers.

Duration of the study: 12 months after the first dose of vaccine/placebo.
A DSMB (see Section 10) will implement blinded interim analyzes regularly, analyzing whether there is a statistically significant difference in the number of COVID-19 cases in one group and another. In that case, they will consider opening the blind. If this analysis shows a clear efficacy in favor of the vaccine, the study may be stopped early to proceed with the vaccination of the placebo group. In such event, the safety and immunogenicity monitoring will be completed as planned.
Study visits: 7 remote or at the clinic visits (details in Section 6 and Tables N°1 and N°2)
Vaccination Schedule: two doses of vaccine/placebo at days 0 and 14
Data collection: data will be collected through an electronic Case Report Form (eCRF)
Follow-Up: all participants will be evaluated and follow up for safety and efficacy. A subgroup of 300 subjects will be follow-up for immunogenicity (225 from the study vaccine arm and 75 from the placebo arm). This group will be included in the center of the Sponsor institution.
Details of safety, immunogenicity and efficacy follow-up, operational definitions, and end points, in Section 7.

4. Study population

In the first part of the study, the study population will consist on 3,000 adult health workers who work with COVID19 patients, male and female (similar proportions of each gender), who have not had a symptomatic and documented previous SARS-CoV-2 infection and in good health (if they have chronic conditions they must be compensated and stable). Pregnant, breastfeeding women or persons with immunosuppressive conditions will not be included. A pregnancy test will be done before each vaccine dose.

If at the 4 months' follow-up, an insufficient COVID19 cases have been recorded, a second group of 2,000 participants will be enrolled. This group will be selected using incidence rates available at that moment (more health workers, people living in counties with high incidence of COVID19 cases, etc.). A Protocol Amendment with a new version of the Protocol and Informed Consent will be issued if the second phase is decided.

4.1. Inclusion Criteria (for the first phase)

- Adults, men and women, older than 18 years' old
    - Health personnel who provide care or are in contact with possible or confirmed cases of COVID-19;
- Able to understand and sign the informed consent form
- Able to comply with all the study procedures and visits

4.2 Exclusion criteria

1. History symptomatic and confirmed infection of SARS CoV-2;
2. For females: Pregnancy (confirmed by positive rapid urine test), breastfeeding or intent to engage in sexual relations with reproductive intent without use of birth control methods in the three months following vaccination;
3. Known allergy to components of the study vaccine or control;

4. Evidence of neurological, cardiac, pulmonary, hepatic or renal diseases decompensated according to medical history or physical examination. Significant changes in the treatment or hospitalization due to complication of the condition in the last 3 months will be considered decompensated disease;
5. Diseases with impaired immune system including: neoplasms (except basal cell carcinoma), congenital or acquired immunodeficiency and uncontrolled autoimmune diseases according to anamnesis or physical examination;
6. Behavioral, cognitive or psychiatric illness that, in the opinion of the principal investigator or his medical representative, affects the participant's ability to understand and collaborate with the requirements of the study protocol;
7. Use of immunosuppressant therapy regimens within the six months prior to enrollment in the study or planned use within the two years following enrollment. Immunosuppressant therapy regimens include: antineoplastic chemotherapy, radiation therapy and immunosuppressants to induce transplant tolerance, among others；
8. Use of immunosuppressive doses of corticosteroids within the three months prior to the enrollment in the study and planned use of immunosuppressive doses of corticoids within the three months following enrollment in the study. Immunosuppressive doses of corticosteroids will be considered the equivalent prednisone 20 mg/day for adults, for longer than one week. Continued use of topical or inhaled corticosteroids is not considered an immunosuppressant;
9. History of asplenia;
10. History of bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture;
11. Any alcohol or drug abuse over the 12 months prior to enrollment in the study that has caused medical, professional or family problems, indicated by clinical history;
12. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate;
13. Participation in another clinical trial with an investigational product in the six months prior to enrollment in the study or planned participation in another clinical trial within the two years following enrollment;
14. Received live attenuated virus vaccine or inactivated vaccine within the 28 days or 14 days, respectively, prior to enrollment in the study, or immunization planned within the 28 days after enrollment in the study;
15. Previous participation in a COVID-19 vaccine evaluation study or previous exposure to a COVID-19 vaccine;
16. Fever (axillary temperature >37.8℃) within the past 24 hours;
17. Any other condition that, in the opinion of the principal investigator or his/her representative physician, could put the safety/rights of potential participants at risk or prevent them from complying with this protocol.

Note: conditions as smoking and obesity.

5. Study Vaccine and Placebo

Each subject will receive two doses of 0,5 ml in the deltoid area of the study vaccine or placebo, with a 14 days' interval between doses. Different arms will be used for both administrations.
Both products have been manufactured by Sinovac Life Sciences Co., Ltd.
Address: N°39 Shangdi Xi Road, Haidian District, Beijing, PRC.

5.1. Investigational vaccine

Study vaccine composition:
SARS-CoV-2 vaccine (Vero cell) inactivated contains inactivated SARS-CoV-2 antigen, aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride. No preservative is present in this product.
0,5 mL/syringe per dose. One pre-filled syringe per box
Description: a milky white suspension
Storage and transport at +2 to +8°C and protect from light. Do not freeze.

5.2. Placebo control

Placebo composition:
Placebo contains aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride. No preservative is present in this product.
0,5 mL/syringe per dose. One pre-filled syringe per box
Description: a milky white suspension
Storage and transport at +2 to +8°C and protect from light. Do not freeze.

5.3. Randomization process

The Company that will provide the electronic support will be responsible for the randomization of the vaccine or placebo in accordance to the protocol, including the sealed envelope system in the electronic CRF (eCRF). This system allows to include multiple randomization criteria. For this study the following variables will be included

- Study site: identification of the immune subgroup (UC site) and allocation of one arm with 225 vaccine receivers and 75 placebo receivers.
- Ratio of placebo vaccine to allow a 1:1 ratio for the total participants

In this way, a randomization list will be created through the "Sealed Envelope" software. The eCRF will be allocating these lists as the site continues to enroll and randomize. The system will always identify the center of each subject, as well as its gender. Then, the system will provide a randomization number, and the subject will be allocated to one of the arms of the treatment. The non-blind team with access will be able to see the arm of treatment in the screen of the eCRF.

5.4. Labeling and blind process keeping for the administration of the investigational product (vaccine or placebo)

The investigational product will be available in a secondary container, an individual box that will contain a prefilled syringe with vaccine or placebo, labeled at the manufacturing site in Sinovac, China. This label will be different for vaccine and placebo boxes. For this reason, a non-blind team will handle the investigational product and will not participate in any other activities with the subjects. As for the administration of the vaccine or placebo, once a subject is randomized and a number is assigned, he or she will be allocated to one of the arms, vaccine or placebo. This information will be only accessible to the non-blind team, who will have restricted access protected by a password. Nobody in the blind team will have access to this information.
The non-blind staff will adhere a new label to the box with the randomization number and will administer the product.

5.5. Vaccine/placebo administration:

A non-blind study nurse will be responsible for the administration of the vaccine/placebo to subjects enrolled into the study according to the protocol procedures. All vaccines/placebo will be administered only by personnel who are qualified to perform that function under applicable local

laws and regulations. These personnel will not perform any safety or efficacy follow-up. Vaccine/placebo will be administered intramuscularly in the deltoid area, following the usual protocols. Each dos will be administered in a different arm.

5.6. Indications / contraindications /warnings /precautions

Until licensed is obtained the vaccine adsorbed inactivated Sinovac vaccine is only for investigational purposes and should only be administered to subjects participating in clinical trial approved by local regulations and ERC as well as inclusion and exclusion criteria defined in the protocol. Since potential adverse events are unknown for this vaccine, there might be a higher risk of AE if there is in use another investigational product. For this reason, subjects participating in this CT should not participate in another investigational product protocol.

5.7. Medications not allowed recommended or forbidden

There are no forbidden medications, but the recommendation is not to use the following medications during 28 days' post vaccine administration:

- Any medication or vaccine not included in this study
- Chronic administration of steroids defined as 10mg/day or more of prednisone for 14 days or more or any immunosuppressive drug
- Any authorized vaccine (other than SARS-CoV-2 vaccine);
- Immunoglobulins or blood products

If the use of any of these products in the first four weeks (28 days) after vaccination is essential, it must occur under medical supervision and be documented in the participant's record. If the use occurred after the first dose and before the second dose, the second dose will not be administered.

5.8. Procedure for availability of vaccine against SARS-CoV-2 in the country

If during the study, the health authority in Chile authorizes the use of this or another vaccine against SARS-CoV-2, the responsible investigator will provide the participants with this new information, and they may request to know if they received a vaccine or a placebo to decide to receive the licensed vaccine. In this case, the blind will be opened for that participant and they will be informed. If it is the Sinovac vaccine, it will be administered ahead of schedule to those who received placebo. If it is another vaccine, the participant may decide to withdraw from the study and receive that product.

This situation will be notified by the Medical Direction of the study to the Ethics Committees, Sinovac, the DSMB and the ISP.

6. Study Procedures

6.1. Study visits

Informed consent must be obtained from the subject prior to the performance of any trial specific tests or evaluations.

Visit 1. AT THE CLINIC. Study Day 0, First dose of vaccine/placebo

a. A detailed explanation of the protocol and written informed consent is obtained. This is done by de investigator or a qualified physician defined by de investigator
b. Demographic data medical history as well as medication in use are requested
c. Details on the risk of COVID19 infection are requested: type of activity, unit of work, time at that work since march 2020

d. Physical Examination(PE) including general and system evaluations. Vital signs recording Arterial blood pressure, height/weight (BMI calculation), axillary temperature. This will be done by de investigator or a qualified physician defined by de investigator
e. Women of childbearing age will be assessed for potential pregnancy. A compromise of birth control for a valid method will be requested to the participant for at least 2 months after the last vaccine dose. If sexually active she must be using a birth control method at least 2 months before the enrolment
f. In women of childbearing age, pregnancy test in urine
g. Inclusion and exclusion criteria evaluation. If the subject meets all inclusion and none exclusion criteria and is confirmed for study enrolment, assign the subject number
h. Randomization for the immunogenicity group (300 subjects) and for vaccine/placebo
i. Blood sample (5 mL) for serology (anti SARS-CoV-2 IgG) and initial measurement of humoral and cellular (50 mL) immune response in the immunogenicity group
j. In childbearing women, a pregnancy test will be done
k. A nasopharyngeal RT PCR will be performed
l. Vaccine administration: a non-blind experienced nurse administers the vaccine/placebo in the deltoid region.
m. The subject is observed for at least 60 minutes, with examination of the injection site to detect local reactions as well as fever, systemic reactions or other adverse event (AE)
n. Give to the subject a thermometer and a ruler to be used for the duration of the study and instruct him/her in its use
o. Written and oral instructions will be provided to the subject for the registration of information in the electronic CRF (eCRF). The system allows the subject to have remote access to register the information that he/she must complete daily until 28 days after the second dose (local and systemic solicited AE 7 days after each dose and then just in case of one of this AE persist, plus other AE, medications, SAE, events of special interest and symptoms of COVID19) and after, until the end of the study (relevant medications, SAE, events of special interest and symptoms of COVID19. Participants are instructed in completing the complete information during the 7 days after each dose at aprox. the same hour each day. They are informed that the system will send daily reminders via email and SMS to their cell phone until day 28 after dose 2 of vaccine/placebo and then, weekly until the end of the study
p. A reminder is given to the need to inform immediately to the study personnel in case of concerning event including SAE and COVID19 symptoms
q. Remote Visit 2 and 3, are scheduled

If there is a temporal exclusion criterion, the subject could be re-scheduled when the condition is not present anymore.

If a participant had a positive PCR upon admission, they will be contacted and monitored by the research team. If he/she remains asymptomatic, he/she can receive the second dose. But, if he/she presents symptoms, he will fall into the exclusion criteria for acute illness and will not receive the second dose.

Participants with symptomatic SARS-CoV-2 infection between doses 1 and 2 of vaccine / placebo, will not receive the second dose, but will continue in the study. The investigator will follow the course of the infection until resolution and will keep safety follow up until the end of study. If the subject belongs to the immunogenicity group and agrees, he/she will continue to participate in the procedures scheduled for this group. These cases will not be included in the efficacy analysis per protocol.

Visit 2. REMOTE: Study Day 7 (+ 2), 7 days after first dose of vaccine/placebo

a. Participant must have completed the daily information od days 0-6 post Dose 1 of vaccine/placebo through remote application (via computer or mobile phone)
b. In the following days, the site personnel review the information, confirm completeness of solicited and unsolicited AEs, concomitant medications and SARS-CoV-2 symptoms.
c. The site personnel contact the subject by phone if needed to complete information
d. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable
e. Schedule Visit 3 (dose 2 of vaccine/placebo) (at the clinic) is confirmed

Visit 3. AT THE CLINIC: 14 days (+14) after first dose - Second dose of vaccine/placebo

a. Participant must have completed the daily information od days 0-6 post Dose 1 of vaccine/placebo through remote application (via computer or mobile phone) or during the visit
b. The site personnel review the information, and confirm completeness
c. Medical history and brief physical evaluation, including measurement of vital signs and axillary temperature. Verify the if the subject has taken any analgesic/antipyretic medication prior to study vaccination
d. In women of childbearing age, pregnancy test in urine
e. Inclusion and exclusion criteria are verified
f. Obtain a blood sample 50 mL via venipuncture in the immunogenicity group
g. Vaccine administration: a qualified study nurse will administer the assigned vaccine intramuscularly in the subject's deltoid area of the other arm
h. Observation of the subject for at least 60 minutes, examination of the vaccination site for any local reactions, subject body temperature, evaluation of any systemic reactions and other AEs
i. A reminder is given to the need of filling the complete safety information and symptoms of COVID19 and that the system will sent regular reminders, according the required frequency
j. Instructions are given to the subject to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms
k. Schedule Visit 4 (D21) (remote)

Visit 4. REMOTE: Study Day 21 (± 2), 7 days after second dose of vaccine/placebo

a. Participant must have completed the daily information of days 0-6 post Dose 1 of vaccine/placebo through remote application (via computer or mobile phone)
b. In the following days, the site personnel review the information, and confirm completeness
c. The site personnel contact the subject by phone if needed to complete information
d. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable
e. Schedule Visit 5-2 (14 days after the second dose) and Visit 5-2 (28 days after the second dose) at the clinic, for the immunogenicity group and Visit 5, remote, for the non-immunogenicity group

Visit 5-1. AT THE CLINIC: 14 (± 4) days after second dose. For the immunogenicity group

a. Participant must have completed the daily information of days 7-13 post Dose 2 of vaccine/placebo by the remote application (via computer or mobile phone) or during the visit
b. The site personnel review the information, and confirm completeness

c. Medical history (including symptoms of COVID19 and contact with a confirmed case) and brief physical evaluation, including measurement of vital signs, axillary temperature, and a check of general appearance
d. Obtain a blood sample (50mL) via venipuncture
e. A reminder is given to the need of filling the complete safety information and symptoms of COVID19 and that the system will sent regular reminders, according the required frequency. Instructions are given to the subject to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms
f. Schedule Visit 5-2, at the clinic (28 days after the second dose)

Visit 5-2. AT THE CLINIC: 28 (+4) days after second dose. For the immunogenicity group

a. Participant must have completed the daily information of days 14-27 post Dose 2 of vaccine/placebo by the remote application (via computer or mobile phone) or during the visit
b. The site personnel review the information, and confirm completeness
c. Medical history (including symptoms of COVID19 and contact with a confirmed case) and brief physical evaluation, including measurement of vital signs, axillary temperature, and a check of general appearance
d. Obtain a blood sample (50mL) via venipuncture
e. A reminder is given to the need of filling the complete safety information and symptoms of COVID19 and that the system will sent regular reminders, according the required frequency. Instructions are given to the subject to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms
f. Schedule Visit 6, at the clinic (180 days after first Dose)

Visit 5. REMOTE: 28 (+4) days after second dose. For the non-immunogenicity group

a. Participant must have completed the daily information of days 7-27 post Dose 2 of vaccine/placebo by the remote application (via computer or mobile phone)
b. The site personnel review the information and confirm completeness
c. The site personnel contact the subject by phone if needed to complete information
d. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable
e. Schedule Visit 6, remote (180 days after first Dose)

FOLLOW-UP PERIOD 1. REMOTE. Since 28 days after Dose 2 to until 179 days after Dose 1

a. Participant must complete the information corresponding to that period by the remote application (via computer or mobile phone): relevant medications, SAE, events of special interest and symptoms of COVID19. They will receive weekly reminders through e-mail or SMS messages to their mobile phone
a. The site personnel contact the subject by phone if needed to complete information
b. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable

VISIT 6. AT THE CLINIC: 180 (±14) days after first dose of vaccine/placebo. For the Immunogenicity group

a. Participant must have completed the information corresponded to that period by the remote application or during the visit

b. The site personnel review the information and confirm completeness
c. Medical history and brief physical evaluation, including measurement of vital signs, axillary temperature, and a check of general appearance
d. Obtain a blood sample (50mL) via venipuncture
e. A reminder is given to the need of filling the complete safety information and symptoms of COVID19 and that the system will sent regular reminders, according the required frequency. Instructions are given to the subject to notify the study personnel immediately if the subject experiences any events that concern the subject or if he/she presents any SARS-CoV-2 symptoms
f. Schedule Visit 7 (D360 post Dose 1 of vaccine/placebo), last visit

Visit 6. REMOTE: 180 days after first dose of vaccine/placebo. For the non-immunogenicity group

a. Participant must have completed the information corresponded to that period by the remote application or during the visit
b. The site personnel review the information and confirm completeness
c. Schedule Visit 7 (D360 post Dose 1 of vaccine/placebo), last visit

FOLLOW-UP PERIOD 2. REMOTE. Since 180 until 359 days after Dose 1

a. Participant must complete the information corresponding to that period by the remote application (via computer or mobile phone): relevant medications, SAE, events of special interest and symptoms of COVID19. They will receive weekly reminders through e-mail or SMS messages to their mobile phone
b. The site personnel contact the subject by phone if needed to complete information
c. The site personnel contact the subject by phone to schedule a visit for performing a RT-PCR for SARS-CoV-2 if applicable

VISIT 7. AT THE CLINIC: 360 (±14) days after first Dose of vaccine/placebo

a. Participant must have completed the information corresponded to that period by the remote application (via computer or mobile phone) or during the visit: relevant medications, SAE, events of special interest and symptoms of COVID19
b. The site personnel review the information and confirm completeness
c. Medical history and brief physical evaluation, including measurement of vital signs, axillary temperature, and a check of general appearance
d. Obtain a blood sample (50 mL) via venipuncture for the immunogenicity subgroup
e. Study close

Table 1. Summary of Study procedures for the Immunogenicity group

Visit	**Visit 1 At the clinic**	**Visit 2 Remote**	**Visit 3 At the clinic**	**Visit 4 Remote**	**Visit 5-1 and 5-2 At the clinic**	**FU Remote**	**Visit 6 At the clinic**	**FU Remote**	**Visit 7 At the clinic**
Procedures and Evaluations/Days	**D0 Dose1**	**Dose 1+7**	**Dose 1+14 Dose2**	**Dose 2 + 7**	**5-1: Dose 2+14 5-2: Dose 2+28**	**Dose 2 +29- Dose 1 +179**	**D180**	**D181-359**	**D360**
Visit window	**V1**	**(+2) V1+7-9**	**(+14) V1+14-28**	**(+2) V3+7-9**	**(+4) V3+14-18 V3+28-32**	**V3+29 to V1+179**	**(±14) V1+166-194**	**V1+180 to 359**	**(±14) V1+346-374**
Enrolment									
Informed Consent	X								
Demographic data	X								
Medical History	X		X		X		X		X
Physical Examination	X		X		X		X		X
SARS CoV-2 IgG	X								
SARS CoV-2 RT-PCR	X								
Inclusion/Exclusion criteria evaluation	X		X						
Investigation product									
Randomization	X								
Vaccination (vaccine/placebo)	X		X						
Safety									
Pregnancy test (urine)*	X		X						
Post vaccination AE**	X		X						
Solicited & Unsolicited AE, CM	X	X	X	X					
Other AE					X				
Relevant CM					X	X	X	X	X
Serious Adverse Event (SAE)	X	X	X	X	X	X	X	X	X
Events of special interest	X	X	X	X	X	X	X	X	X
Efficacy									
Efficacy assessment by clinical data and SARS CoV-2 RT-PCR when correspond	X	X	X	X	X	X	X	X	X
Immunogenicity									
Cellular and humoral immune response to SARS-2	X				X		X		X
Safety & Efficacy Registration									
Information to be registered by the participant in the eCRF		D0-6 post Dose 1	D7-13 post Dose1	D0-6 post Dosis 2	D7-28 post Dose 2	D29 post Dose 2-179 post Dose 1		D180-360 post Dose 1	

Table 2. Summary of Study procedures for the non-immunogenicity group

Visit	**Visit 1 At the clinic**	**Visit 2 Remote**	**Visit 3 At the clinic**	**Visit 4 Remote**	**Visit 5 Remote**	**Follow-Up Remote**	**Visit 6 Remote**	**Follow-Up Remote**	**Visit 7 At the clinic**
Procedures and Evaluations/Days	**D0 Dose1**	**Dose 1 + 7**	**Dose 1 + 14 Dose2**	**Dose 2 + 7**	**Dose 2 + 28**	**Dose 2 +29- Dose 1 +179**	**D180**	**D181-359**	**D360**
Visit window	**V1**	**(+2) V1+7-9**	**(+14) V1+14-28**	**(+2) V3+7-9**	**(+4) V3+28-32**	**V3+29 to V1+179**	**(±14) V1+166-194**	**V1+180 to 359**	**(±14) V1+346-374**
Screening/Enrolment									
Informed Consent	X								
Demographic data	X								
Medical History	X		X						X
Physical Examination	X		X						X
SARS CoV-2 IgG	X								
SARS CoV-2 RT-PCR	X								
Inclusion/Exclusion criteria evaluation	X		X						
Investigation product									
Randomization	X								
Vaccination (vaccine/placebo)	X		X						
Safety									
Pregnancy test (urine)*	X		X						
Post vaccination AE**	X		X						
Solicited & Unsolicited AE, CM	X	X	X	X					
Other AE					X				
Relevant CM					X	X	X	X	X
Serious Adverse Event (SAE)	X	X	X	X	X	X	X	X	X
Events of special interest	X	X	X	X	X	X	X	X	X
Efficacy									
Efficacy assessment by clinical data and SARS CoV-2 RT-PCR when correspond	X	X	X	X	X	X	X	X	X
Safety & Efficacy Registration									
Information to be registered by the participant in the eCRF	D0-6 post Dose 1	D7-13 post Dose 1	D0-6 post Dose 2	D7-28 post Dose 2	D29 post Dose 2-179 post Dose 1	D180-360 post Dose 1			

CM: concomitant medications; AE: adverse events; SAE: serious adverse events
*All female subjects of childbearing potential must test negative for pregnancy during screening and at visits prior to study vaccine administration.
**Subjects will be observed for at least 30 minutes after the administration of study vaccine for local and general symptoms or reactions.

6.2. Procedure in case of loss of contact or visit

If a subject does not attend a visit o there is no contact in the period established by the protocol the investigator will continue attempts to contact and identify the reason for this as well as the clinical condition and will try to schedule a new visit resuming the rest of the visits. These attempts will be registered and must be done with a 2-week interval

6.3. Withdrawal of the subject

The following reasons are causes for withdrawal:

- Subject Consent withdrawal. Subject can do it at any time without any penalty
- Investigator withdrawal. In case of any situation that puts the subject at risk or it is deemed the subject cannot finish the protocol
    - Anaphylactic reaction with the first vaccine dose
    - SAE with the first vaccine dose
    - Subject gets pregnant between dose 1 and 2
    - Any event that can jeopardize safety of the subject
    - Address change or other situation that avoids complying with the study procedures

Any withdrawal will be registered in the study file and in section protocol end documenting the reasons for this subjects will not be replaced.

6.4. Criteria for temporary detention of the Study:

The following events will cause a temporary study stop:

• Death of a participant, in which there is no obvious alternative cause

• SAE or events of special interest, two or more episodes of anaphylaxis (pregnancy excluded), in which there is no obvious alternative cause

The detention will be decided by the Medical Director who will inform the centers, the DSMB, the institutional ethics committee (each IR must inform their local ethics committees), Sinovac and Public Health Institute. The DSMB will conduct an un-blinded analysis of the case, if it deems it appropriate, and will make written recommendations on whether or not to continue the study.

The resumption of the study in the centers will occur once the written notification is received from the Medical Director of the study. The DSMB may stop the study due to other situations or events that in its judgment put the safety of the participants at risk.

In case of suspension of the administration of the research product, the participants will continue with their safety evaluations, and new parameters may be added as necessary to prevent possible risks.

7. Efficacy, Safety and Immunogenicity Evaluation

7.1 Evaluation and follow-up

7.1.1. Safety: All vaccinated subjects will be observed on site for immediate adverse events (AEs) for 60 minutes after vaccination. Solicited local or systemic AEs occurring ≤7 days after each dose will be recorded in a Daily Cards (D0-6 and D14-20). Medications and all AEs occurring up to 28 days after Dose 2 and SAE and events of special interest occurring 360 days after Dose 1 will be recorded by participants through a remote application and its completeness will be verified by study personnel.

An independent Data Safety Monitoring Board (DSMB) will assess the safety and reactogenicity data of the first 100 subjects when they complete a 7 day of follow up after each vaccine dose and then

at regular intervals. The DMSB is empowered to halt the trial temporarily and prevent further vaccination in case the analysis indicates considerable safety issues.
All SAE and events of special interest must be reported by the Responsible Investigator to the Medical Director, to the center monitor, and to local ethics committee in 24 hours from the date when the study site team becomes aware of the event. The Medical Director will report any SAE to the DSMB, the Public Health Institute (ISP) and to Sinovac. The DMSB could stop the study temporary or even prevent the administration of more vaccines if the event suggests any relevant safety problem.

7.1.2. Efficacy: subjects will be followed up until 12 months after the first dose to identify and register any SARS-CoV-2 infection. COVID19 symptoms will be collected through the informatics platform and in-site visits. Participants will be instructed to report to the study team through the electronic platform, e-mail, cell phone message or telephone call, each time they fulfill the suspected case definition (see definition below). In those cases, they will be scheduled for evaluation by a study physician, since the third day of symptoms, to perform a RT-PCR in nasopharyngeal (NP) sample. If this RT-PCR results negative, a second one will be performed at least 48 h after the first. This visit will be registered as a non- scheduled visit.

Participants with SARS-CoV-2 infection will be evaluated by a study physician, including a complete physical examination and oxygen saturation, and they will receive the driving directions that correspond to their particular clinical situation. Their evolution will be closely monitored by the research personnel until the resolution of the picture, the same will be done in the case of hospitalization.
Severity and duration of each sign and symptom will be recorded. The severity of the COVID19 symptoms will be classified indicated in Table 3, based on the guides “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials” from the United States Food and Drug Administration (FDA) and in the “Common Terminology Criteria for Adverse Events - Version 5.0” guide by the United States National Cancer Institute (NCI / NIH).
In addition, intensity of the condition will be registered using the scale of clinical progression indicated in the Table 4, based on the WHO recommendations (Marshall et al, 2020). For grading other symptoms, the scale indicated in Table 6 and 7 of the Safety Section will be used. The follow-up of outpatients will be done by phone calls, with special attention in early detection of symptoms of alarm COVID19 associated, to offer the medical advice corresponding to the clinical condition of the patient. If it is necessary, home visit could be performed for a better evaluation of the patient. The clinical management will follow the local guidelines according the severity of the case. Hospitalized patients will be monitored daily to verify his/her evolution according the clinical scale, but the management will be performed by the hospital team. For outpatients, the presence and maximum severity of each symptom will be registered.

COVID19 case monitoring will be conducted since the enrolment, but just the cases occurring 14 days after final vaccination will be considered valid cases for per protocol efficacy analysis.

Table 3. Classification of the severity of signs and symptoms with suspicion of COVID-19

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Respiratory rate	17-20 breaths per minute	21-25 breaths per minute	>25 breaths per minute	Intubation
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental activities of daily living	Shortness of breath at rest; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	
Anosmia	Present	-----	-----	-----
Dysgeusia / Ageusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-----	-----
Illness or clinical adverse event (as defined according to applicable regulations) and other signs and symptoms	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Visit to the emergency room* OR Hospitalization

Table 4. Scale of clinical progression of SARS-CoV-2 infection. Adapted from the WHO proposal (Marshall et al).

Description	Score
Non infected, viral RNA no detected	**0**
Asymptomatic, viral RNA detected	**1**
Symptomatic, independent	**2**
Symptomatic, assistance needed	**3**
Hospitalized, no oxygen therapy	**4**
Hospitalized, oxygen by mask or nasal prongs	**5**
Hospitalized, oxygen by non-invasive ventilation or high flow	**6**
Intubation and mechanical ventilation, pO2/FiO2 ≥150 or SpO2/FiO2 ≥200	**7**
Mechanical ventilation pO2/FIO2	**8**
Mechanical ventilation pO2/FiO2	**9**
Death	**10**

7.1.3. Immunogenicity: blood samples will be collected from participant in a subgroup of 300 out of the first 3,000 participants (225 from the study vaccine arm and 75 from de placebo arm) at D0 (first dose day, baseline), 14 and 28 days after first dose and 14 and 28 days after the second dose to determine the neutralizing antibody level, percentage of seroconversion, and cellular immunity; and at D180 and D360 for determine persistence of immune response.

7.1.4. Remote follow up: due to pandemic mobility restriction measures, the majority of visits will be remote, using an application for the participant's register and sending the needed information to the eCRF. Regular reminders will be sent by this application. At any suspected case of COVID19 an in-site visit will be scheduled to obtain a RT-PCR for SARS-CoV-2 by NP swab. If this RT-PCR results negative, a second one will be performed at least 48 h after the first.

7.2. Efficacy Analysis

Efficacy Endpoints:
All end points will be compared between vaccinated and placebo recipients

- Number of cases of SARS-CoV-2 infection confirmed by PCR from 14 days after the second dose of vaccine
- Number of cases only received one dose of SARS-CoV-2 infection confirmed by PCR from 14 days after vaccine
- Number of cases of clinically diagnosed SARS-CoV-2 infection from 14 days after the second dose of vaccine
- Number of hospitalized cases of SARS-CoV-2 infection from 14 days after the second dose of vaccine
- Number of pneumonia cases of SARS-CoV-2 infection from 14 days after the second dose of vaccine
- Number of severe or death cases of SARS-CoV-2 infection from 14 days after the second dose of vaccine

Efficacy Operational definitions
Suspected COVID-19 case:
The definition of case surveillance for 2019 coronavirus disease (COVID-19) that will be used in this study will be that stated by FDA guides, as follows:
Anyone who has at least one of the following symptoms will be able to have a diagnostic RT-PCR test for SARS-CoV-2:

- Fever or chills;
- Cough;
- Shortness of breath or difficulty in breathing;
- Fatigue;
- Muscle or body pain;
- Headache;
- Loss of smell or new taste;
- Sore throat;
- nasal congestion or runny nose;
- Nausea or vomiting;
- Diarrhea.

The definition of symptoms is subjective and depends on what each participant considers abnormal for their routine condition. It is recommended to evaluate all participants as soon as possible since the third of presentation of these symptoms, although collection is allowed until the fourteenth day after the onset of symptoms.

Laboratory criteria
Detection of SARS-CoV-2 nucleic acid in a clinical sample.

Classification of cases
Possible:
Anyone who meets the clinical criteria.
Confirmed case:
Anyone who meets the laboratory criteria.
Discarded case:
Refers to all possible cases of COVID-19 that had two negative RT-PCR diagnoses two days apart and collected during the 14 days after the onset of symptoms.

Severity criteria of RT-PCR confirmed symptomatic COVID-19:
- Mild Disease: Symptomatic patients without viral pneumonia or hypoxia
- Moderate Disease: Clinical signs of pneumonia (fever, cough, shortness of breath, difficulty breathing) but no signs of severe pneumonia, SpO2 ≥ 90% on room air
- Severe disease: Clinical signs at rest indicative of severe clinical illness (RR≥30/min, HR≥125/min, sat ≤93% at room air at sea level, PaO2/FiO2 < 300 mm Hg); respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO); evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors) o Significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; death

Any detected COVID19 case will be reported in this trial and in the National Surveillance System (EPIVIGILA) and will be treated and managed according to the Chilean Guidelines. Clinical management of cases will be providing for the participant 'own health system. A close follow-up of the outcome of any COVID19 case will be done by the study team, registering new symptoms, severity grading, therapies, hospitalization, intensive care admission, complications, mechanical ventilation use, sequelae and death.

Criteria for determining vaccine efficacy will be to reach a protection of at least 50% according the target product profile proposed by the WHO and the Guidelines for COVID-19 vaccine of the US FDA. Success of the efficacy criteria will be reach if the sequential monitoring of the symptomatic virologically confirmed COVID-19 cases results in a lower limit adjusted 95% confidence interval over 30% of efficacy.

7.3. Safety Analysis
Safety Endpoints
- Incidence of local (pain, induration, swelling, redness, pruritus) and systemic (diarrhea, anorexia, vomiting, nausea, muscle pain (non-inoculated site), arthralgia, headache, cough, fatigue, pruritus (non-inoculated site), skin rash (exanthema), allergic reaction, fever (axillary temperature)) solicited reactions until 28 days after the second dose of the vaccine/placebo, stratified by age group (18-59 and ≥ 60 years old)
- Incidence of any adverse event (AE) until 28 days after second dose of vaccine/placebo

- Incidence of SAE and events of special interest until 12 months after the first dose of the vaccine
- SAE, events of special interest or AE leading to withdrawal from the study
- Concomitant medications until 28 days after the second dose of the vaccine/placebo
- Relevant concomitant medications (immunosuppressive or immune modulating drugs, other drugs or vaccine in investigation, transfusions of blood products, immunoglobulins, other vaccines) since 29 days after the second dose up to the end of the study

Adverse Events Definitions, Severity Grading and Study Vaccine Relationship:
Adverse Events: an adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.
An unexpected adverse event is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.
All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and medical monitor whether continued follow-up of the AE is warranted.

The investigator should include in his / her assessment of adverse events:

- The classification of its intensity;
- The classification of its severity;
- The classification of its causal association with the product under investigation;
- The measures taken;
- Its evolution.

Severity of AE: The severity of solicited AE will be graded through a numeric scale of 1 to 4, as per Table 5 (local events) and Table 6 (systemic events), created based on the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" guide of the Food and Drug Administration of the United States (FDA), the "Common Terminology Criteria for Adverse Events - Version 5.0" of the National Cancer Institute of the United States (NCI/NIH).

Table 3. Severity grading criteria for local adverse events

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Pain at the site of the investigational product administration	Does not interfere with daily activities	Repeated use of non-narcotic pain reliever > 24 hours OR interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Visit to the emergency room* OR Hospitalization
Erythema at the site of investigational product administration†	25 – 50 mm	51 – 100 mm	> 100 mm	Necrosis OR Exfoliative dermatitis
Swelling at the site of investigational product administration†	25 – 50 mm	51 – 100 mm OR interferes with activity	> 100 mm OR prevents daily activity	Necrosis
Induration at the site of investigational product administration†	25 – 50 mm	51 – 100 mm OR interferes with activity	> 100 mm OR prevents daily activity	Necrosis
Pruritus at the site of investigational product administration	Does not interfere with daily activities	Interferes with activity	Prevents daily activity	Visit to the emergency room* OR Hospitalization

The maximum measured diameter or area should be used for induration and swelling, and red; evaluation and grading should be based on functional grade and actual measurement results, and higher grading indicators should be selected.

Table 4. Severity grading criteria for systemic adverse events and vital signs

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Fever	37.8 – 38.4°C	38.5 – 38.9°C	39.0 – 40.0°C	>40°C
Nausea	Does not interfere with daily activities OR 1 to 2 episodes in 24 hours	Interferes slightly with daily activities OR More than 2 episodes in 24 hours	Prevents daily activities, requires intravenous hydration	Visit to the emergency room* OR Hospitalization for hypovolemic shock
Vomiting	Does not interfere with daily activities OR 1 to 2 episodes in 24 hours	Interferes slightly with daily activities OR More than 2 episodes in 24 hours	Prevents daily activities, requires intravenous hydration	Visit to the emergency room* OR Hospitalization OR Hypovolemic shock
Diarrhea	2 – 3 loose stools in 24 hours	4 – 5 stools in 24 hours	6 or more watery stools or requires outpatient IV hydration	Visit to the emergency room* OR Hospitalization
Headache	Does not interfere with daily activities	Repeated use of non-narcotic pain reliever > 24 hours OR Interferes slightly with daily activities	Significant; any use of narcotic pain reliever or prevents daily activity	Visit to the emergency room* OR Hospitalization
Fatigue	Does not interfere with daily activities	Some interference with activity	Significant; prevents daily activity	Visit to the emergency room* OR Hospitalization
Myalgia	Does not interfere with daily activities	Some interference with activity	Significant; prevents daily activity	Visit to the emergency room* OR Hospitalization
Chills	Feeling slightly cold; chills, teeth chattering	Moderate whole body shivering, requires use of opioids	Severe or prolonged, does not respond to opioids	-----

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or Total parenteral nutrition indicated	-----
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental activities of daily living	Severe symptoms; limiting self-care activities of daily living	-----
Arthralgia	Mild pain	Moderate pain; limiting instrumental activities of daily living	Severe pain; limiting self-care activities of daily living	-----
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental activities of daily living	Widespread and constant; limiting self-care activities of daily living or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-----
Skin rash (exanthema)[†]	Present, but asymptomatic	Symptomatic (pruritus/pain), but interferes only slightly with daily activities	Symptomatic, prevents daily activities	Visit to the emergency room* OR Hospitalization
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated

[†]Specify if the skin rash is located in any specific body part or if it is widespread.

The severity of the unsolicited clinical adverse events will be classified through a numeric scale of 1 to 5, as per Table 7, which was created based on the "Guidelines for classification of adverse events in vaccine clinical trials" of the FDA-NIH.

Table 7. Severity grading criteria for unsolicited adverse events.

GRADE 1 (Mild)	Transient (< 48 hours) or mild discomfort; no medical intervention/therapy required
GRADE 2 (Moderate)	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3 (Severe)	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4 (Life-threatening)	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
GRADE 5	Death

Relationship evaluation:
All adverse events should be classified by the principal investigator or his medical representative as to their causal relationship with the product under investigation, according to the classification adapted from the "Uppsala Monitoring Center" of the World Health Organization (WHO-UMC), described in Table 8.
Medical Director may request additional clarifications from the responsible investigator to justify the causal relationship attributed to the event. The causal relationship may also be reviewed at the request of the Independent Data and Safety Monitoring Committee upon written justification. All local reactions after administration of the product under investigation will be considered as adverse events with a certain causal relationship to vaccination.

Table 8. Classification of causal relationship of Adverse Events with the investigational product

Reasonable causal relationship			Causal relationship NOT reasonable	
Adverse Event considered as Adverse Reaction			Adverse Event cannot be considered as Adverse Reaction.	
Certain	**Probable**	**Possible**	**Unlikely**	**Not related**
Event or change (abnormal value) in a laboratory test, with plausible temporal relationship with regarding the administration of the intervention;	A clinical event, including a change (abnormal value) in a laboratory test, with a reasonable temporal relationship regarding the administration of the intervention;	A clinical event, including a change (abnormal value) in a laboratory test, with a reasonable temporal relationship regarding the administration of the intervention;	A clinical event, including a change (abnormal value) in a laboratory test, which, due to the time of the administration of the intervention, gives cause to an unlikely, but not impossible, relationship;	A clinical event, including a change (abnormal value) in a laboratory test, which, due to the time of the administration of the intervention, gives cause to a non-existing relationship;
It cannot be explained by a concurrent disease or another intervention or medication; The event is defined pharmacologically or phenomenologically (i.e., a specific and objective disorder or a pharmacologically recognized phenomenon);	It is unlikely to be caused by a concomitant illness or by another intervention or medication;	It can also be explained by concurrent disease or other interventions or medications;	Another disease or another drug provide a plausible explanation	Another disease or another drug provide a plausible explanation
The response to discontinuation or withdrawal is plausible (pharmacologically, pathologically);	The response to discontinuation or withdrawal is clinically reasonable;	Lack of information or lack of clarity about withdrawal or treatment discontinuation		
Re-exposure is satisfactory, if required	Re-exposure is not required			

Serious Adverse Events Definition and Reporting:

Serious adverse event (SAE):
Any untoward medical occurrence that:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs subject's hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage

- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

SAE Reporting:
All SAE will be reported by the responsible investigator to the local Ethics Committee and to the Medical Director within one (1) calendar day from the date when the study site team becomes aware of the event. The initial notification must not be delayed even if the information is incomplete. Reporting of SAE will be completed preferably through the appropriate form that is included in the CRF system after assessment by a study doctor, or directly if it is not possible to access the CRF, mentioning the contact date and time of the first notification that was made by any means.
Medical Director will be responsible to report to: the DSMB, the institutional Ethics Committee, Sinovac and the Public Health Institute (ISP) in the following 48 h of being notified/or in the time frame defined by each organization.

Definition and Reporting of Events of Special Interest
The urgent reporting of Events of Special Interest aims to inform the sponsor, other investigators and regulatory bodies about new data regarding serious reactions or occurrences that require special monitoring. The Priority List of Adverse Events of Special Interest in COVID-19 vaccines prepared by Brighton Collaboration is included in events of special interest. In this study, the following should be reported as a matter of urgency:

- Serious Adverse Events;
- Confirmed case of COVID-19, including serious cases;
- Pregnancy in the first 4 weeks after the last vaccination;
- Generalized seizure;
- Guillain-Barre syndrome;
- Acute disseminated encephalomyelitis;
- Hematological thrombocytopenia;
- Immune anaphylaxis;
- Vasculitis;
- Other serious local or systemic adverse events after immunization.

Reporting of Events of Special Adverse Event will be done in the same way indicated in the SAE reporting (Section 7.3.5).

Pregnancies:
To ensure subjects' safety, each pregnancy in a subject on study vaccine must be reported by the responsible investigator to their local ethics committee and to the Medical Director within 24 hours of learning of its occurrence. The Medical Director will notify to DSMB, the institutional Ethics Committee, Sinovac and the Public Health Institute (ISP). The pregnancy should be followed up to determine outcome, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
Pregnancies within the first 4 weeks after the last vaccination will be reported as indicated in section Pregnancies that occur afterwards and its follow up will be reported at the end of the study or before it any event of preoccupation is detected, to ethics committees, to DSMB, to Sinovac and to the Public Health Institute (ISP).

7.4. Immunogenicity Analysis

Immunogenicity Endpoints

- Seroconversion rate of IgG of SARS-CoV-2 at 14 and 28 days after the second dose of the vaccine
- Neutralizing antibody of SARS-CoV-2 at 14 and 28 days after the second dose of the vaccine
- GMT and GMI of IgG anti SARS-CoV-2 at 14 and 28 days after the second dose of the vaccine

Exploratory immunogenicity end-points:

- Cellular and humoral immunity in incidental cases of COVID that occurs in the immunogenicity group
- Cellular immunogenicity at 14 and 28 days after each dose of the vaccine
- IgG antibodies and cellular immune response persistence at 180 and 360 days after the first dose of the vaccine

Pairwise comparison:

Pairwise comparisons related to the response after the second dose of vaccine and between vaccine and placebo will be performed in terms of:

• Ratio of GMTs
• Differences of seroconversion rates

Immunogenicity Assays

To evaluate the immune response to the study vaccine, the following assays will be performed in the immunogenicity group of 300 participants:

Evaluation of the humoral immune response generated against SARS-CoV-2:

- Humoral immune response based on total IgG: It will be determined by measuring serum IgG antibodies against Spike protein (S) and nucleoprotein (N). A quantitative ELISA test previously validated. For this, serum from subjects of the immunogenicity group will be obtained on days 0 and 14 and 28 days after each dose.
- Humoral immune response based on neutralizing antibodies: A SINOVAC standardized micro titer methodology will be used, which will be carried out in this company's offices. For this, serum from subjects of the immunogenicity group will be obtained on days 0 and 14 days after first dose and 14 and 28dyas after the second dose. An ELISA-based surrogate method of neutralizing antibody measurement will alternatively be used

Evaluation of the cellular immune response generated against SARS-CoV-2

- ELISpot and flow cytometry techniques will evaluate the T cell response in peripheral blood mononuclear cells of volunteer subjects at Day 0 (baseline state) and 14 days after first dose and 14 and 28 days after second dose. The mononuclear cells will be purified and exposed ex vivo to a mega-pool of peptides derived from SARS-CoV-2 proteins. Specifically, secretion of IFN-γ will be measured by ELISpot (also called Interferon gamma release assay –IGRA). Additionally, the expression of activation markers and immunological memory in CD4 + / CD8 + T cells will be measured, including CD69, CD25, CD71, CD44, among others. As a negative control, the response against a pool of peptides derived from an irrelevant protein produced equivalently to peptides from SARS-CoV-2 proteins will be measured. In addition, CD4 + / CD8 + T cell staining will be included to measure intracellular IFN-γ expression in CD4 + / CD8 + T cells, followed by cell permeabilization and subsequent anti-IFN-γ antibody staining

Evaluation of immune response persistence

- Humoral and cellular response evaluation will be repeated at 180 and 360 days after the first dose for determining the persistence of antibodies

Evaluation of the immune response generated in cases of confirmed SARS-CoV-2 infection:
In subjects from the immunogenicity group with SARS-CoV-2 infection, the humoral and cellular response will be studied in a sample taken days after PCR confirmation.

Humoral immune assays based on total IgG and cellular immune assays will be performed at the Laboratory of Biomedical Molecular Immunology, Virus, Inflammation and Microbial Pathogenesis, Faculty of Biological Sciences.

7. Statistical Plan and Analysis

8.1. SAMPLE SIZE

Adaptive designs are used to calculate the sample size of this trial, and relevant parameters are set as follows:
- Protection rate of the vaccine μ =0.5
- The incidence rate in the high-risk population group: 6%
- α=0.05；
- 1-β=0.9；
At least 1,068 subjects will be recruited in each group. Considering 25% subjects will be missing during the test, the sample size in each group is 1,500.

8.2. ANALYSIS WITH DESCRIPTIVE METHODOLOGY

The numerical variables will be described with arithmetic mean ± standard deviation, median, interquartile range and the minimum and maximum values. The categorical variables will be described with numbers of cases and proportions at each level of the variables. Relevant results will be presented with exact 95% confidence interval.
The same type of descriptive analysis will be done for the demographic, anthropometric and pre-data reference data for SARS-CoV2. To determine the homogeneity of the study groups, they will be compared using Fisher's exact test for binary variables and Wilcoxon's rank test for continuous variables.
The distribution of participants, including the number of people included, selected, randomized, and vaccinated, will be summarized and presented on a Consort diagram, including study discontinuation. The reasons why some subjects did not enroll (failed inclusion or exclusion criteria) and why some volunteers discontinued their participation in the study will be described and summarized.

8.3. PRIMARY EFFICACY ANALYSIS

The efficacy of the vaccine will be evaluated using log-binomial regression to compare efficacy as a dichotomous variable and using the Cox proportional hazards model to evaluate efficacy over time. Both models will include age and sex as stratification variables and an allocation group covariate to compare those who received the vaccine with those who received placebo. The log-binomial model will make it possible to estimate RR (relative risk) and with the Cox model the hazard ratio with a 95% confidence interval, the efficacy of the vaccine (1 - risk index), and the p-values will be estimated. Cumulative incidence charts will also be created with this model.

8.4. SAFETY ANALYSIS

The safety analysis will include all participants who received the study product, vaccine or placebo, together and by age group. The primary safety analysis will consider all adverse events, solicited and unsolicited, with a possible or probable causal relationship with the product that occurred in the first week after its administration. The secondary analysis will extend this period until the fourth week after vaccination. Additionally, unsolicited adverse events with a reasonable causal relationship to the product will be included in further analysis since the fourth week after the second dose and until the end of the follow-up.
All adverse events will be coded and grouped according to MedDRA (Medical Dictionary for Regulatory Activities) methodology.

Solicited adverse events will be analyzed by the proportion of participants with observation of any event and according to the degree and type of event in that group. The set of participants analyzed will correspond to the set of participants for which there are data, eg. for immediate observation after vaccination, it must be confirmed that the participant was observed within 60 minutes after vaccination. The population for the evaluation of reactogenicity will be the one analyzed for the events up to the first and fourth week after vaccination, according to the availability of the Participant Diary. Registered requested adverse events will be presented in a summarized form according to their maximum intensity and duration per participant, when relevant. Rates will be accompanied by exact two-tailed 95% confidence intervals. Rates will be compared between groups using the two-tailed Fisher's exact test, both overall and by type and intensity.

Unsolicited adverse events analyzed will be those that occurred within 28 days after vaccination, except when they are considered SAE, Events of Special Interest or that have a reasonable causal relationship with the vaccination. Unsolicited adverse events will be summarized at the participant level where a participant contributes only once to a type of event with the maximum intensity and / or causal relationship to the product. Additional tables can summarize the number of events of a certain type observed in a group, without considering the number of participants who originated it.
Unsolicited adverse events will be summarized by intensity and causal relationship to vaccination. In the case of SAE, the criteria to be classified as serious will also be recorded. Tables will show unsolicited AE with a frequency of 1% or more. Additional tables will show events that led to the discontinuation of vaccination, those which had an intensity 3 or 4 and SAE. Between age groups, AE rates with a causal relationship to vaccination will be compared using Fisher's exact two-tailed test.

COVID-19 and severe acute respiratory syndrome cases will be compared between the allocation groups in both frequency and intensity. The intensity score will be compared using the Wilcoxon test and the frequency of severe cases of the total events will be compared to verify the difference in proportions between the groups. These comparisons are intended to assess whether there is any possibility of vaccine-enhanced disease. A separate CRF will collect symptoms to determine respiratory disease and the intensity of those symptoms for comparisons between groups, as well as by age and sex.
Reference data, such as the presence of comorbidities, will also be presented between the groups. All pregnancy cases, including the results, will also be described.

8.5. IMMUNOGENICITY ANAYSIS

The immunogenicity analysis will describe the results of the IgG and neutralization tests according to the two age subgroups in terms of seroconversion rates and antibody titers. The geometric means of the titles will also be described among those who seroconvert and will be compared between the participants who acquired COVID-19 infection and a subgroup of those who did not. This information will be reported for each group, vaccine or placebo recipients. The tests will consider the presence of antibody titers before the first vaccination and any documented information of previous infection.

The following descriptive statistics will be calculated for each assessment and each group:

- Seroconversion rates with 95% confidence intervals compared to the pre-vaccination titer
- Median of titles with 95% confidence intervals
- Plots of cumulative reverse distribution of bonds / concentrations
- Box plots of titers / concentrations

8.6. MANAGEMENT OF ABSENT DATA

For the primary efficacy analysis per protocol, no replacements will be assigned to missing data, therefore the analyzes will exclude participants with missing or non-evaluable data. If there is an excessive amount of missing data or some kind of pattern exists between the missing data, the implementation of additional statistical tools would be considered.

8.7. LEVEL OF SIGNIFICANCE AND STATISTICAL SOFTWARE

A significance level $\alpha = 5\%$ will be considered for all statistical comparisons. All analyzes will be done using the statistical programs SAS 9-4 and R 4.0.2.

8.8. Definitions of populations to analyze

To meet the objectives of the study, different data sets will be evaluated according to the nature of the result.

Included Population

All selected participants who signed the informed consent form and were eligible to participate in the study, regardless of whether they were actually randomized or not.

Safety population

All included participants who received at least one dose of study vaccine and have safety data available. In the event of an assignment error, the participant will be analyzed according to the product that they actually received.

Population for reactogenicity evaluation

All participants in the security population who provided complete information on the Daily Cards to assess the requested adverse events. The population is defined for each vaccination (first or second dose) and requires that the participant has actually received the corresponding dose.

Per protocol population (PP)

It includes all randomized participants who: met the inclusion criteria and did not meet any exclusion criteria; received the two doses of the investigational product to which they were assigned under the conditions of handling and administration recommended by the manufacturer; and they did not use drugs restricted by the protocol.

Participants will remain in the per-protocol population until a major deviation occurs (for example, receive another vaccine for COVID-19). The follow-up time elapsed until the moment of the deviation may be included in the analysis of the protocol until the exclusion event. A report will detail the excluded participants, the time of exclusion and the justification. If the participant does not have a relevant study deviation, all his data will contribute until the end of his follow-up. The per protocol analysis is the main analysis of study efficacy.

Intention-to-treat (ITT) population
Includes all randomized participants receiving at least one dose of the product. Participants will be analyzed in the group to which they were assigned and contributed the follow-up time that is available for intention-to-treat analysis. Intention-to-treat analysis is considered a secondary efficacy analysis for this study.

Populations for immunogenicity analysis
The populations for immunogenicity correspond to all the participants of the per protocol population who were assigned to the immunogenicity group and have the laboratory samples to perform the corresponding analyzes.

8.9. PROCEDURES FOR UNBLINDING
Early un-blinding, if necessary, will be requested by the responsible investigator, or his medical representative, and must occur in writing. This may be due to emergency medical issues, legal and / or regulatory requirements, or at the request of a participant if the country has a vaccine against SARS-CoV-2 authorized for use (see Section 5.8). The responsible investigator must document in writing the reasons for the un-blinding and inform the sponsor (Medical Director) within two working days of the occurrence. The blinding will be broken through a specific form sent by the sponsor (Medical Director). The early un-blinding should also be reported in the individual record of the research participant. The sponsor (Medical Director) must report an early blinding break to the Chairman of the Data and Safety Monitoring Committee (described in section 3.15.1) within two business days.
The Data and Safety Monitoring Committee may break the blind code to assess the Safety data of one or more participants. The justification for breaking the blind must be recorded in the minutes of the corresponding meeting. The code that is broken by the Committee will only be revealed to the sponsor and the investigator if it is relevant to the protection of one or more participants in the research.

9. Study Monitoring and Audits
Study monitoring and auditing will be performed in accordance with the local regulatory requirements. Investigators and their study staff will be trained on the study protocol and all applicable study procedures prior to subject enrollment. A CRF (printed and electronic) must be complete for each enrolled subject.
Study progress will be monitored by a Contract Research Organization (CRO) (Activa8 Clinical Research) as frequently as necessary to ensure the rights and well-being of study subjects are protected, to verify adequate, accurate and complete data collection, protocol compliance and to determine that the study is being conducted in conformance with applicable regulatory requirements.
Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

10. Data Management

10.1. Data collection:

Each study participant will have an individual study card or "paper" CRF, which will be used as a source document and which will be labeled with the code assigned to the subject, to maintain the confidentiality of the participants. In this document all the data of the study visits and the medical and nursing procedures will be recorded. All original documents will be kept in the research center safely.
An electronic CRF (eCRF) will be available to collect the study information. Data entry will be performed only by authorized members of the study team using an individual password with electronic signature. eCRF will be stored on a secure server designated by the sponsor.

Safety and efficacy information from participants will be collected through remote via. For doing that, they will receive a link to the system via mail or SMS to their mobile phone. They will be trained for system access and in data entry.

- Days 0-6 post Dose 1 and 2: solicited and unsolicited AE, concomitant medications, SAE, events of special interest
- Days 7-13 post Dose 1: solicited AE (if persist), other AE, concomitant medications, SAE, events of special interest
- Days 7-28 post Dose 2: solicited AE (if persist), other AE, concomitant medications, SAE, events of special interest
- Days 29 post Dose 2 up the end of the study: relevant concomitant medications registration, SAE, events of special interest

Besides this safety information, participants must register and report ti the site if they present symptoms of COVID19.
The application will allow the participants to send the corresponding information at the time of the remote visit or when the mentioned situations present. Reminders will be sent via e-mail and mobile phone daily since dose 1 up to 28 days after dose 2 and weekly thereafter until the end of the study. All the collected information will be review for study personnel for completeness.

For the storage of the electronic data an OpenClinica® Enterprise version 4 software will be used (OpenClinica, Waltham, MA, USA), which will be managed by SemiCrol, Spain, company that give the technical support. The data base for statistical analysis will be extracted directly from OpenClinica® Enterprise software.

10.2. DSMB:

Safety: The DSMB will assess the safety and reactogenicity data of the first 100 subjects when they complete a 7 day of follow up after each vaccine dose; and after that, periodically until the end of the study.
Efficacy: The DSMB will assess the blinded efficacy data by Interim Analyses. If there is less COVID19 cases that needed for efficacy confirmation, the second phase with 2,000 new participants will be set up (adaptive design).
DSMB members: this committee will be constituted by 5 independent experts, that included 3 specialists in infectious diseases, virology, epidemiology, at least one with experience in vaccine clinical trials, one statistician and one administrative secretary.

Members of the committee will be absolutely independent from the sponsor and they will not receive any payment for their participation.
DSMB role: The committee will make written recommendations to continue, modify, suspend or terminate the study if the first analysis or any further reveals any considerable safety issues, or if the interim analysis shows vaccine efficacy. These recommendations will be received by the sponsor and communicated to the researchers for apply it and to inform to the respective Research Ethics Committees.

11. Ethics

11.1 Regulatory and Ethical Compliance:

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (Laws 19.628; 20.120; 20.584; 20.850 and the Chilean Sanitary Code, Law 20.850, that modifies the Chilean Sanitary Code), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Informed Consent Procedures:

Eligible subjects may only be included in the study after providing written and witnessed by a representative of the Institution Director, informed consent approved by the Institutional Ethics Committee
Informed consent must be obtained by trained medical study personnel, before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.
In case that employees or students from health or educational institutions linked to research centers may be invited to participate in the study, it will be checked whether the potential participant has any dependency relationship with the principal investigator or with the discipline to which the principal investigator belongs. In such cases, the right to refuse without any penalties is guaranteed. This statement must be indicated in any text of invitation to participate of the study.

11.3. Protocol Amendments:

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects.
An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes).
Protocol amendments must be approved by the IRB/IEC/REB.
As the study has an adaptive design, if the second phase with new 2,000 participants is decided, and Amendment and a new version of the Informed Consent will be submitted and approved by the Ethical Committee and by the Chilean Public Health Institute (ISP).
In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol.

11.4. Insurance and health coverage for possible damages

There will be an Insurance to cover health attentions that may occur due to the presentation of any damage derived from the study vaccine.

The conditions are as follows: the insurer is responsible for paying the costs and expenses of the claimants with respect to any claim made by the research subjects for an injury caused by the trial (investigational product or study procedures). Insurance does not cover costs associated with acquiring a possible SARS-CoV-2 infection.

Considering that any SAE or event of particular relevance that needs insurance coverage will be reported to the DSMB, to the ethics committees and to the Chilean Public Health Institute, in the event of any conflict that may arise when defining the insurance application, there will be several other entities that may ensure the good of the participant.

Besides that, and at all times, the participants, family and/or their legal assistant can request insurance coverage.

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